Annex 1 to TOX/2025/23

Annex 1 to TOX/2025/23

Executive Summary

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This is a draft position statement for discussion. This does not represent the views of the Committee and should not be cited.

Statement on the derivation of a health-based guidance value for antimony First draft statement

Secretariat

April 2025

Executive Summary

1. Post European Union (EU) exit, the Drinking Water Inspectorate (DWI) is reviewing the regulatory standards for some chemicals in drinking water, including antimony. The UK Health Security Agency (UKHSA) sought advice of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) with respect to an appropriate health-based guidance value (HBGV) for antimony.

2. The World Health Organization (WHO), the US Agency for Toxic Substances and Disease Registry (ATSDR) and Health Canada have used the same study (Poon et al., 1998) to derive different HBGVs. The differences are primarily due to variations in the interpretation of the study findings, particularly in the choice of the No Observed Adverse Effect Level (NOAEL).

3. The COT agreed that the Poon et al. (1998) study was the most appropriate study to use to derive a HBGV for antimony. The COT determined that the NOAEL of 6,000 micrograms per kilogram of body weight per day (µg/kg bw/day), based on decreased body weight gain and reduced food and water consumption in adult rats, was the point of departure. An uncertainty factor (UF) of 300 was recommended, resulting in a tolerable daily intake (TDI) of 20 µg Sb/kg bw/day as a HBGV for antimony.

Background and scope of discussion

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7. Overall Conclusion - Annex 1 to TOX/2025/23
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4. The UKHSA advises the DWI on potential health risks from chemicals in drinking water. Post EU exit, the DWI is reviewing the regulatory standards for some chemicals in drinking water, including antimony. UKHSA sought advice from the COT with respect to an appropriate HBGV for antimony, which would inform the consideration of an appropriate drinking water regulatory limit for antimony.

5. The COT has previously reviewed the dietary exposure to antimony in infants and young children aged 4 to 18 months as part of the 2014 survey of metals and other elements in infant foods (COT, 2017). The COT has also reviewed dietary exposure to antimony in various population subgroups as part of the 2006 UK Total Diet study of metals and other elements (COT, 2006). For these reviews, the COT used the WHO TDI of 6 µg/kg bw/day for the evaluation (WHO, 2003).

6. More recently Health Canada (2024) and ATSDR (2019) have considered antimony and derived lower HBGVs. WHO, ATSDR and Health Canada all derived their HBGVs from the same study (Poon et al., 1998), however, they diverge in their interpretation of the study results and the selection of the NOAEL.

7. Two antimony discussion papers (TOX/2024/38 and TOX/2025/04) were presented to the COT at the October 2024 and February 2025 meetings respectively. The COT assessed the Poon et al. (1998) study and its interpretations, as well as other available evidence in order to determine an appropriate HBGV to support an update to the antimony drinking water standard in the UK.

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Properties of antimony and sources in drinking wate

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8. Antimony (Sb, CAS number: 7440-36-0) is a silvery white metal naturally present in the Earth's crust (Sundar and Chakravarty, 2010). The most common source of antimony in drinking water appears to be dissolution from metal plumbing and fittings (WHO, 2003). Antimony compounds can exist in trivalent (Sb^{3+}) and pentavalent (Sb^{5+}) states, with trivalent antimony being considered more toxic than pentavalent antimony. In drinking water, pentavalent antimony is the more prevalent form of antimony. However, some evidence suggests that both can coexist and cycle between each other under certain conditions (Health Canada, 2024). For further information on the properties of antimony, see TOX/2024/38 and TOX/2025/04.

Oral toxicity data for antimony - Annex 1 to TOX/2025/23

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Poon et al. 1998 study and interpretation

9. In the study by Poon et al. (1998), groups of 15 male and 15 female Sprague-Dawley rats were exposed to 0, 0.5, 5, 50, or 500 parts per million (ppm) antimony as antimony potassium tartrate (APT, 99.95% pure) in drinking water for 13 weeks. Based on average water consumption and body weight data, the investigators calculated antimony doses of 0, 60, 560, 5,580 and 42,170 µg/kg bw/day in males and 0, 60, 640, 6,130 and 45,690 µg/kg bw/day in females. An additional group of 10 male and 10 female rats was exposed to 0 or 500 ppm (0 and 42,170 µg/kg bw/day for males and 45,690 µg/kg bw/day for females) for 13 weeks followed by a 4-week recovery period.

10. A dose-dependent reduction (15–17%) in serum glucose levels in females exposed to doses greater than or equal to 640 µg Sb/kg bw/day was observed. Lower glucose values were also observed in the males; however, these were not statistically different from controls.

11. Other toxicological endpoints were identified by the study at the highest antimony doses in males and females (42,170 or 45,690 µg Sb/kg bw/day). These included a decrease in water and food consumption, a decrease in body weight gain (significant in males starting at week 6 and females at week 12), haematological changes which differed between males and females, decreases in serum creatinine levels and alkaline phosphatase levels, and liver effects including changes in activity of some liver enzymes such as ethoxyresorufin-O-deethylase (EROD) and glutathione-S-transferase (GST).

12. Anisokaryosis in the liver was observed in all antimony-exposed groups, with a dose-related increase in the severity observed.

13. Other hepatic effects included an increase in hepatocellular portal density in all antimony-exposed groups, but this was considered mild in males and females at greater than or equal to 560 and 640 µg Sb/kg bw/day respectively. Minimal nuclear hyperchromicity was also observed at these levels but with no consistent dose-response relationship.

14. In terms of skeletal effects, an increase in myeloid hyperplasia in the bone marrow was observed at ≥5,580 µg Sb/kg bw/day in males and ≥640 µg Sb/kg bw/day in females.

15. Spleen effects included sinus congestion at ≥560 µg Sb/kg bw/day in males, sinus hyperplasia at 42,170 µg Sb/kg bw/day in males and ≥640 µg Sb/kg bw/day in females and arterial cuff atrophy at 42,170 µg Sb/kg bw/day in males. In the recovery period, increases in incidence of sinus congestion (males only), arterial cuff atrophy, periarteriolar lymphocyte sheath cell density and sinus haematopoiesis were observed.

16. The study authors concluded 0.5 ppm antimony in drinking water, equivalent to an average intake of 60 µg Sb/kg bw/day, as the NOAEL for this study, primarily based on the statistically significant dose-dependent decrease in serum glucose levels in females at ≥640 µg Sb/kg bw/day.

17. Lynch et al. (1999) reviewed the Poon et al. (1998) study and provided an alternative interpretation of the observed toxicological effects. The authors stated that the observed effects at lower doses were either adaptive or non-toxicological in nature. They considered that some of the histological findings, particularly in the liver, spleen and thyroid, should not be considered toxicologically relevant and proposed a higher NOAEL. Lynch et al. (1999) proposed that the NOAEL for the study should be set at 50 ppm, equivalent to an

average intake of 6,000 Sb µg/kg bw/day, based on the finding of decreased body weight gain and decreased food and water consumption at the 500 ppm dose level (though they stated that these effects may be due to the nonpalatability of the drinking water).

18. Valli et al. (2000), from the same group as Poon et al. (1998), maintained that the NOAEL of 60 µg/kg bw/day, as identified by Poon et al. (1998), was appropriate given the observed liver and spleen histology and serum biochemistry alterations. Valli et al. (2000) stated that the higher NOAEL of 6,000 µg/kg bw/day proposed by Lynch et al. (1999) underestimated the potential for early signs of toxicity and was not sufficiently protective.

Further oral antimony studies with NOAELs less than 6000 µg/kg bw/day

19. Marmo et al. (1987), Rossi et al. (1987) and Angrisani et al. (1988) reported findings from an antimony exposure study in NOS Albino normotensive rats.

20. Rossi et al. (1987) reported a NOAEL in maternal rats of 70 µg Sb/kg bw/day. This was due to a significant dose-dependent decrease in maternal body weight by gestation day 20 following prenatal oral exposure to antimony trichloride. It should be noted, however, that basal maternal body weights for each treatment group on day 0 of gestation prior to exposure were approximately 7% lower than the control group. Thus, the reported 8 to 10% deficit (in the low- and high- dose groups respectively) from controls seen on gestation day 20 represents a relatively small change from the 7% deficit at the start of gestation. The pup lowest observed adverse effect level (LOAEL) was reported as 700 µg Sb/kg bw/day due to decreases in body weight (Rossi et al., 1987).

21. Additional findings reported by Marmo et al. (1987) noted decreased vasomotor reactivity due to both prenatal and postnatal oral exposure to antimony trichloride. Additional findings reported by Angrisani et al. (1988) showed postnatal exposure to antimony trichloride did not affect maternal or pup body weights or systolic arterial blood pressure.

22. In a study conducted by Kanisawa and Schroeder (1969), life term oral exposure to 5 ppm antimony as potassium tartrate (equivalent to 350 µg Sb/kg bw/day) in mice did not result in a significant difference in the incidences of spontaneous tumours or malignant tumours compared to controls. The authors

identified 350 µg Sb/kg bw/day as the NOAEL for this study.

23. In a lifetime exposure study conducted by Schroeder et al. (1970), a significant reduction in survival rates and reduced non-fasting glucose levels were identified when rats were exposed to 430 µg Sb/kg bw/day potassium tartrate in their drinking water. The authors reported a LOAEL of 430 µg Sb/kg bw/day based on these effects.

24. Annex A provides further detail on the available antimony toxicity studies with comments on the Committees consideration of the reported NOAELs.

HBGVs established by WHO, ATSDR and Health Canada

In this guide

25. WHO selected a NOAEL of 6,000 µg Sb/kg bw/day from the Poon et al. (1998) study, as recommended by Lynch et al. (1999), for decreased body weight gain and reduced food and water intake. A UF of 1,000 (100 for interspecies and intraspecies differences and 10 for the short duration of the study) was applied to the NOAEL resulting in the TDI of 6.0 µg/kg bw/day (WHO 2003).

26. ATSDR selected a NOAEL of 60 µg Sb/kg bw/day for decreases in serum glucose levels in female rats observed in the Poon et al. (1998). A UF of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to derive an intermediate-duration (15 – 365 days) oral Minimal Risk Level (MRL) of 0.6 µg/kg bw/day (ATSDR 2019).

27. Health Canada also selected a NOAEL of 60 µg Sb /kg bw/day from the study by Poon et al. (1998), based on observed histopathological changes in the liver (anisokaryosis) and alterations in serum biochemistry indicative of liver effects. A UF of 300 was applied (10 for interspecies variation, 10 for intraspecies variation and 3 for the use of a subchronic study) resulting in a TDI of 0.2 µg/kg bw/day (Health Canada, 2024).

28. More information on the derivation of the HBGVs for WHO, ATSDR and Health Canada is available in the COT discussion paper TOX/2024/38.

Discussion

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8. List of abbreviations and their full meanings - Annex 1 to TOX/2025/23
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29. The COT determined that the effects on serum glucose levels in female rats observed in Poon et al. (1998), which informed the NOAELs selected by ATSDR and Health Canada, showed limited dose-response. The Committee also noted that an intraperitoneal study by the National Toxicology Program (NTP) which examined antimony at higher doses and with greater bioavailability did not observe these effects (NTP 1992).

30. The Committee further agreed that the liver changes observed in Poon et al. (1998), which also informed the NOAEL selected by Health Canada, were minor and not indicative of adverse effects as there was no evidence of increase in liver weight across a large range of doses. The changes in the levels of liver enzymes were deemed to be minor and inconsistent with a hepatotoxic effect. The Poon et al. (1998) study showed no clear evidence of changes in thyroid hormone effects and there was also difficulty in interpreting spleen findings due to high background variation and the findings were not considered to be of toxicological significance.

31. The Committee agreed with the Lynch et al. (1999) interpretation that the significant body weight changes observed at the highest dose in Poon et al. (1998) was critical effect. Therefore, the COT determined a NOAEL of 6,000 µg/kg bw/day for this study.

32. With respect to other oral studies with doses less than the NOAEL determined by COT for the Poon et al. (1998) study, the COT noted that the baseline maternal body weight in the study by Rossi et al. (1987) at gestation day 0 was approximately 7% lower in treated groups compared to controls. Consequently, the observed 8–10% reduction in maternal body weight at gestation day 20 used as the basis for the maternal NOAEL was considered a relatively small change, given the pre-existing baseline differences. The Committee noted that the NTP intraperitoneal study observed body weight effects only at the highest dose (9,600 µg Sb/kg bw/day).

33. The COT further observed that while decreased pup body weight was reported in the Rossi et al. (1987) study in the high dose group, the investigation by Angrisani et al. (1998) antimony exposure found no significant changes in pup body weight. With the lower initial maternal body weights in the treated groups reported in the Rossi et al. (1987) study, it was suggested that the observed lower body weight in prenatally exposed pups could be secondary to the lower maternal body weights of this group rather than a direct effect of antimony on pups. For these reasons, the lower NOAEL and LOAEL (when compared to the 6,000 µg Sb/kg bw/day NOAEL from the Poon et al. (1998) study) relating to maternal and pup body weight reported in the Rossi et al. (1987) study were discounted.

34. There were concerns regarding the reliability of the studies by Kanisawa and Schroeder (1969) and Schroeder (1970) and challenges interpreting their data. Furthermore, the nature of these studies does not allow for the demonstration of a dose-response, therefore the NOAELs and LOAELs reported in these studies were also discounted.

Overall Conclusion

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35. Overall, the COT concluded that the NOAEL of 6,000 µg Sb/kg bw/day, from the Poon et al. (1998) study based on decreased body weight gain and reduced food and water consumption in adult rats, was the appropriate point of departure to use as the basis of a HBGV for antimony.

36. The Committee also highlighted that the pentavalent form of antimony, which is predominant in drinking water, exhibits lower toxicity compared to the trivalent form. As Poon et al. (1998) utilized the trivalent form of antimony (antimony potassium tartrate) in their study, a HBGV derived from the NOAEL of 6,000 µg Sb/kg bw/day was considered a sufficiently protective for antimony in drinking water.

37. The Committee recommended a UF of 300, comprising a factor of 10 for interspecies variation, 10 for intraspecies variation, and 3 for subchronic to chronic extrapolation. This results in a TDI of 20 µg Sb/kg bw/day.

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List of abbreviations and their full meanings

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µg Sb/kg bw/day	Micrograms of antimony per kilogram of body weight per day
APT	Antimony Potassium Tartrate
ATSDR	Agency for Toxic Substances and Disease Registry
bw	Body Weight
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
DWI	Drinking Water Inspectorate
EROD	Ethoxyresorufin-O-deethylase
EU	European Union
GST	Glutathione-S-transferase
HBGV	Health-based guidance value
LOAEL	Lowest Observed Adverse Effect Level - the lowest dose in a study at which adverse effect(s) are observed.

mg	Milligram
µg	Microgram
MRL	Minimal Risk Level - an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure
NOAEL	No Observed Adverse Effect Level - the highest administered dose at which no adverse effect has been observed.
NTP	National Toxicology Program
POD	Point of Departure
ppm	Parts per million
Sb	Antimony
TDI	Tolerable Daily Intake - an estimate of the amount of a contaminant, expressed on a body weight basis (e.g., mg/kg body weight) that can be ingested over a lifetime without appreciable health risk.
UF	Uncertainty factor
UKHSA	United Kingdom Health Security Agency
WHO	World Health Organization

References

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Annex A

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Statement on the derivation of a health-based guidance value for antimony to support development of UK Drinking Water Standards

Table 1. Summary of antimony toxicity studies and comments on the derived NOAELs.

Author and year	Study details	Dose level	Findings	No observed adverse effect level (NOAEL)	Comments the NOAEL

			Dose-dependent decrease in serum glucose levels in females at ≥640 µg Sb/kg bw/day. Decrease also noted in males but not statistically significant.	
Species: Sprague-Dawley rats. **Route of exposure:** Oral-Drinking water.	**Initial Study Original Dose:** 0, 0.5, 5, 50, or 500 ppm antimony potassium		decrease in water and food consumption, a decrease in body weight gain (significant in males starting at week 6 and females at week 12), haematological changes which differed between males and females, decreases in serum creatinine levels and alkaline phosphatase levels, and liver effects including changes to liver enzyme activity all observed at the highest antimony dose (42,170/45,690 µg Sb/kg bw/day in males and females	**Poon et al. (1998) recommend** **NOAEL:** NOA is based on decreased in serum glucos levels in females at ≥640 µg Sb/ bw/day. However, the Committee determined t these effects showed limit dose-respons The Committ noted that ar

			Prenatal and Postnatal exposure: Decreased antihypotensive response to norepinephrine and hypotensive response to isoprenaline at both dose levels in 60-day old rats. The hypotensive response to acetylcholine was decreased at the highest dose of antimony trichloride in 60-day old rats. No change in antihypotensive or hypotensive responses was seen in 30-day old rats.		
Marmo et al. (1987)	**Species:** NOS Albino normotensive rats. **Route of exposure:** Oral-Drinking water. **Study duration:** Maternal exposure: - 1st day of pregnancy until weaning (22nd day after delivery) or from PND1 to PND 22. Pups: - From weaning until 30 or 60 days of age. **No/Sex:** 30	**Original Dose:** 1 and 10 mg/L antimony trichloride. **Recalculated Dose Levels:** 70 and 700 µg Sb/kg bw/day.	**Postnatal exposure: -** 60-day-old offspring in the high-dose group showed reduced antihypotensive responses to carotid artery occlusion and norepinephrine injection, as well as reduced hypotensive responses to	70 µg Sb/kg bw/day. Pup LOAEL: 700 µg Sb/kg bw/day.	See Rossi et (1987)

Rossi et al. (1987)	**Species:** NOS Albino normotensive rats. **Route of exposure:** Oral-Drinking water. **Study duration:** Prenatal: 1st day of pregnancy until weaning (22nd day	**Original Dose**: 1 and 10 mg/L antimony trichloride. **Recalculated**	**Both doses**: Maternal body weight decreased significantly in a dose-dependent manner by the 20th day of gestation. **High dose:** Pups had decreased BW; No macroscopic teratogenic	Maternal NOAEL: 70 µg Sb/kg bw/day. Pup LOAEL: 700	NOAEL is bas on dose-dependent decrease in maternal boc weight by gestation da 20 following prenatal oral antimony exposure. Th COT noted th the baseline maternal boc weight in the study by Ros et al. (1987) gestation da was approximate 7% lower in treated grou compared to controls. Consequentl the observed 8–10% reduction in maternal boc weight at gestation da 20 used as th basis for the maternal NO was consider a relatively small change given the pre existing baseline differences. With the lowe maternal boc

Angrisani et al. (1987)	**Species:** NOS Albino normotensive rats. **Route of exposure:** Oral-Drinking water. **Study duration:** Postnatal: From PND1 to PND60. **No/Sex:** 30 per group Rat offspring: - 10 pups/ group, equal sex ratio.	**Original Dose:** 1 and 10 mg/L antimony trichloride. **Recalculated Dose Levels:** 70 and 700 µg Sb/kg bw/day	Postnatal exposure to antimony trichloride did not affect maternal or pup body weights or systolic arterial blood pressure. No macroscopic teratogenic effects have been observed. Antimony exposure did not significantly affect the length of gestation, and number of newborns per litter.	Maternal NOAEL: 70 µg Sb/kg bw/day. Pup LOAEL: 700 µg Sb/kg bw/day.	See Rossi et (1987)

Kanisawa and Schroeder (1969)	**Species:** Mice (White Swiss, Charles River CD-1). **Route of exposure:** Oral-Drinking water. **Study duration:** Lifetime exposure. **No/Sex:** Control mice – 71; Antimony treatment – 76.	**Original Dose** : 5 ppm Antimony Potassium Tartrate. **Recalculated Dose Level:** 350 µg Sb/kg bw/day.	Compared to control, significant differences in the incidences of spontaneous tumors and malignant tumors did not appear. Female mice had shorter life spans when given antimony than their controls. Fatty degeneration of liver noticed in both control (22.2%) and antimony fed groups (15.9 %).	350 µg Sb/kg bw/day.	The COT rais concerns regarding th reliability of t data and challenges interpreting t data. Furthermore the nature of this study do not allow for demonstratio of a dose-response, therefore the NOAEL was discounted.

			Negligible effects on growth and mature weight. Antimony was not tumorigenic.		
Schroeder et al. (1970)	**Species:** Long Evan Rats. **Route of exposure:** Oral-Drinking water. **Study duration:** 2 years. **No/Sex**: Not reported.	**Original Dose:** 5 ppm - Antimony Potassium Tartrate (APT). **Recalculated Dose Level:** 430 µg Sb/kg bw/day.	Decrease in survival rate. Antimony, however, was innately toxic, males surviving 106 days and females 107 days less than the controls at median life spans, and 70 and 165 days less when 90% were dead; Hearts of males fed antimony weighed 18.9% less than their respective controls, whereas the hearts of females weighed 3.5% more. Decreased non-fasting serum glucose levels. Non fasting glucose levels were lower than fasting ones in the antimony group. Glycosuria was found in 23% of 90 controls, 43%	LOAEL: 430 µg Sb/kg bw/day.	The COT rais concerns regarding th reliability of t data and challenges interpreting t data. Furthermore the nature of this study do not allow for demonstratio of a dose-response, therefore the LOAEL was discounted.

NTP (1992)	**Species:** B6C3F1 Mice **Route of exposure:** Intraperitoneal injection. **Study duration**: 13 weeks. **No/Sex:** 10 Males per group. 10 Females per group.	**Original Dose:** 0, 1.5, 3, 6, 12 and 24 mg/kg antimony potassium tartrate; 3 times per week. **Recalculated Dose Levels:** 0, 600, 1,200, 2,400, 4,800 and 9,600 µg Sb/kg bw/day.	High dose: Body weights were reduced by about 10% compared to controls (not statistically significant). Hematological analyses revealed decreases in red blood cell counts and hemoglobin of both sexes of high-dose mice at week 7 and again at week 13 for the red blood cell counts. In association with these changes was increased absolute and relative spleen weight.	4,800 µg Sb/kg bw/day.	The dose wa given intraperitone therefore thi study was nc used for the determinatio of the appropriate NOAEL for or antimony consumption

			Mortality was observed in 4 of 10 male rats in the highest dose groups. A reduction in body weight was seen in both male (18%) and female (11%) rats from these groups.		
NTP (1992)	**Species:** F344/N rats. **Route of exposure:** Intraperitoneal injection. **Study duration:** 13 weeks. **No/Sex:** 10 Males per group. 10 Females per group.	**Original Dose:** 0, 1.5, 3, 6, 12 and 24 mg/kg antimony potassium tartrate; 3 times per week. **Recalculated Dose Levels:** 0, 600, 1,200, 2,400, 4,800 and 9,600 µg Sb/kg bw/day.	Relative liver weight was increased in male and female rats from all dose groups (maximum increase of 20% for males and 40% for females at 9600 µg Sb/kg bw/day). Dose-related increases in serum alanine aminotransferase and sorbitol dehydrogenase were also observed in male and female rats. Hepatocellular degeneration and necrosis were observed in male rats and in female rats. Kidney	1,200 µg Sb/kg bw/day.	The dose wa given intraperitone therefore thi study was nc used for the determinatio of the appropriate NOAEL for or antimony consumption

Sunagawa (1981)	**Species:** Wistar rats. **Route of exposure:** Oral-Feeding. **Study duration:** 24 weeks. **No/Sex:** 5 per dose.	**Original Dose**: Metallic Antimony: 0, 0.5, 1.0, 2.0%. Antimony Trioxide: 0, 1.0, 2.0%. **Recalculated Dose Levels:** Metallic Antimony: 0, 500,000, 1,000,000, 2,000,000 µg Sb/kg bw/day. Antimony Trioxide: 0, 418,000, 836,000 µg Sb/kg bw/day.	Metallic antimony high dose: decreased body weight gain. Metallic antimony high dose: decreased hematocrit and hemoglobin. Antimony trioxide all dose: decreased erythrocyte levels. Metallic antimony mid and high dose: slight cloudy swelling in hepatic cords. Antimony trioxide all dose: slight cloudy swelling in hepatic cords.	LOAEL: 418,000 µg Sb/kg bw/day.	The LOAEL is higher than t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo antimony.

			BW gain decreased for all. The weight of the rats of each 1.0%-Sb and 1.0%-Sb2O3 groups was lighter than that of 0.1%-Sb group.		
Hiraoka (1986)	**Species:** Wistar rats. **Route of exposure:** Oral-Feeding. **Study duration:** 12 weeks. 12 weeks recovery. **No/Sex**: 12 males per group.	**Original Dose:** Metallic Antimony: 0.1% (w/w), 1.0% (w/w) o. Antimony Trioxide: 1.0% (w/w). **Recalculated Dose Levels:** Metallic Antimony: 85,000, 850,000 µg Sb/kg bw/day. Antimony Trioxide: 700,000 µg Sb/kg bw/day.	Recovery animal-increased in weight up to the normal level. Some significant changes of the organ weight and the ratio between organ weight and body weight of the rats, after the administration of Sb and Sb2O3; 1.0%-Sb: decreased haemtocrit. 0.1%-Sb: no changes in Hb, AST and albumin to globulin ratio. 0.1%-Sb: increased ALT. 1.0%-Sb: decreased total protein levels; High concentrations of antimony were found in liver,	700,000 µg Sb/kg bw/day.	The NOAEL is higher than t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo antimony.

			Maternal and fetal body weights were reduced in the high-dose group (18% and 10%, respectively, at 300,000 µg Sb/kg/day). Embryo lethality was also observed in this dose group (decreased number of live fetuses).		
Miranda et al. (2006)	**Species:** Wistar rats. **Route of exposure:** Subcutaneous injection. **Study duration**: GD1 – 20. **No/Sex:** 19-21/group.	**Original Dose:** 0, 75, 150, 300 mg SbV/kg bw/day Meglumine antimoniate. **Recalculated Dose Levels:** 0, 75,000, 150,000 or 300,000 µg Sb/kg/day.	The frequency of dilated ureter was increased in fetuses from the 150,000 and 300,000 µg Sb/kg/day dose groups. Skeletal variations were also seen in the mid- and high-dose groups (misaligned sternebrae, supernumerary ribs, misshapened basiooccipital bone). Transplacental transfer of antimony was confirmed by	75,000 µg Sb/kg/day.	The LOAEL is higher than t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo antimony.

Hext et al. (1999)	**Species:** Wistar rats. **Route of exposure:** Oral-Feeding. **Study duration:** 90 days. **No/Sex:** 12 Males per group.	**Original Dose:** 0, 1,000, 5,000, 20,000 ppm antimony trioxide. **Recalculated Dose Levels:** Males: 0, 70,000, 353,000, 1,408,000 µg Sb/kg bw/day. Females: 0,	Absolute and relative liver weights were increased by approximately 10% in female rats fed 20,000 ppm antimony trioxide; Elevated red cell count in high-dose male rats (+4%) and a decreased mean cell volume in high-dose female rats (-2%); Triglyceride content was increased (+30%) and alkaline phosphatase activity was decreased (-12%) in high-dose male rats. High-dose female rats exhibited an increase in plasma cholesterol (+13%), a decrease in alkaline phosphatase activity (-36%) and an increase in aspartate aminotransferase activity (+52%). Alkaline phosphatase	1,408,000 µg Sb/kg bw/day (male rats) and 1,570,000 µg Sb/kg bw/day (female rats).	The NOAELs higher than t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo

Coelho et al. (2014)	**Species:** Pregnant female Wistar rats. Route of exposure: Subcutaneous injection. **Study duration:** Gestation Day 0-PND 21. No/Sex: Control - 14; Treatment - 16 per dose.	Original Dose: 0, 75, 150, 300 mg SbV/kg bw/day of meglumine antimoniate. **Recalculated Dose Levels:** 0, 75,000, 150,000, 300,000 µg SbV/kg bw/day.	At the highest dose, MA reduced the birth weight and the number of viable newborns. In the male offspring, MA did not impair development (somatic, reflex maturation, weight gain, puberty onset, open field test), sperm count, or reproductive performance. Except for a minor effect on body weight gain and vertical exploration in the open field, MA also did not affect the development of female offspring. Measurements of the Sb levels in the blood of MA-treated female rats and their offspring demonstrated that Sb is transferred to the fetuses via the placenta and to the suckling pups via milk.	150,000 µg SbV/kg bw/day.	The dose wa given via subcutaneou injection therefore thi study was no used for the determinatio of the appropriate NOAEL for or antimony consumption

		Reduction (P<0.05) in foetal birth weight and litter size was observed as compared to the control. High dose of SSG & MA: - Death of all animals before completion of the treatment; Skeletal anomalies were restricted to the formation of a rudimentary 14th rib. Haematoma was only seen in the extremities of foetuses born to antimony treated animals.	
Species: Sprague	**Original Dose Levels:** 1. Sodium Stibogluconate (SSG): 30,000,	Treatment of pregnant rats with SSG (30,000 µg Sb/kg) daily for 10 successive days, starting on day 6 of gestation, exhibited a 5.9% foetal resorption rate. This effect seems to be dose dependent as doses of 100,000 and	The dose wa

Omura et al. (2002)	**Species:** Wistar rats, CD-1 mice. **Route of exposure:** Oral-gavage feeding. **Study duration:** 4 weeks. **No/Sex:** Rats: 7 to 8 per group. Mice: 8-10 per group.	Original dose: 1.Antimony Potassium Tartrate group: 27.4 mg/kg body weight. 2.Low-Antimony trioxide group: 12 mg/kg body weight 3.High-Antimony trioxide group: 1,200 mg/kg body weight. Recalculated dose levels: 1.Antimony Potassium Tartrate group: 10,000 µg Sb/kg bw/day. 2.Low-Antimony trioxide group: 10,000 µg Sb/kg bw/day. 3. High-Antimony trioxide group: 1,000,000 µg Sb/kg bw/day.	1. Three mice (1 control, 2 given 1,200,000 µg/kg-day) died due to gavage error; Sperm parameters were not affected by neither compounds and histopathology results were essentially negative.	1,000,000 µg Sb/kg bw/day.	The NOAEL is higher than t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo antimony.

Belyaeva (1967)	**Species:** Rats (not specified). **Route of exposure:** Inhalation. **Study duration:** 1.5-2 months, 4 hours/day. **No/Sex:** 10-24/group.	**Original Dose:** 0 and 209,000 µg Sb/m^3 antimony trioxide. **Recalculated Dose Levels**: 0 and 209,000 µg Sb/m^3.	No changes in body weight gain were noted. Fetal body weights remained unchanged. Unspecified lesions were reported in the lungs, liver, kidneys, and pancreas. Reproductive effects, including failure to conceive and uterine metaplasia, were observed. However, a decrease in fertility and reduced number of offspring was found in rats exposed to 209 mg Sb/m^3 of antimony trioxide before conception and during gestation.	209,000 µg Sb/m^3.	The dose wa given via inhalation therefore thi study was nc used for the determinatio of the appropriate NOAEL for or antimony consumption

REACH registration dossier submitted to ECHA (2014)	**Species:** Sprague-Dawley rats. **Route of exposure:** Oral-Drinking water. **Study duration:** Gestation days 6-19. **No/Sex:** 2 females per dose.	**Original Dose:** 0, 100, 300 and 1000 mg/kg bw/day sodium hexahydroxo-antimonate. **Recalculated Dose Levels:** 0, 49,000, 148,000, 493,000 µg Sb/kg bw/day.	Increased (non-significant) incidence in delayed skeletal development were observed in the mid and high dose groups. When considering skeletal malformations overall, incidence was observed in 99.3% to 100% of fetuses and 100% of litters including controls.	49,000 µg Sb/kg bw per day.	The NOAEL is higher than t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo antimony.

Annex A Reference

In this guide

7. Overall Conclusion - Annex 1 to TOX/2025/23
8. List of abbreviations and their full meanings - Annex 1 to TOX/2025/23
9. References - Annex 1 to TOX/2025/23
10. Annex A - Annex 1 to TOX/2025/23
11. Annex A References - Annex 1 to TOX/2025/23

This is a draft position statement for discussion. This does not represent the views of the Committee and should not be cited.

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